THE AMENDMENTS

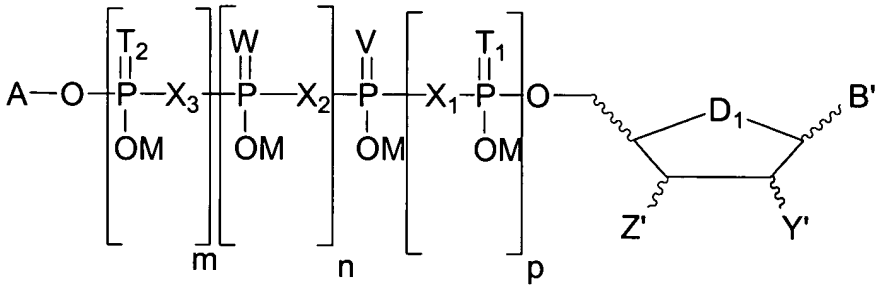
In the Claims

1-2 (Canceled)

3. (Previous Presented) A method of preventing or treating diseases or conditions associated with platelet aggregation comprising:

administering to a subject a pharmaceutical composition comprising a therapeutically effective amount of a $P2Y_{12}$ receptor antagonist compound, wherein said amount is effective to bind $P2Y_{12}$ receptors on platelets and inhibit ADP-induced platelet aggregation, wherein said $P2Y_{12}$ receptor antagonist compound is a dinucleotide compound of Formula I, or salts thereof:

Formula I



wherein:

X_1, X_2, and X_3 are independently oxygen, methylene, monochloromethylene, dichloromethylene, monofluoromethylene, difluoromethylene, or imido;

T_1, T_2, W, and V are independently oxygen or sulfur;

m= 0, 1 or 2;

n= 0 or 1;

p= 0, 1, or 2 ;

where the sum of m+n+p is from 0 to 5;

M =H or a pharmaceutically-acceptable inorganic or organic counterion;

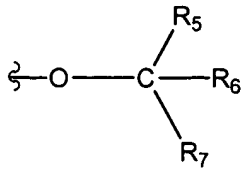
D_1 =O;

Y' =OR_1;

Z' =OR_2;

R_1 and R_2 are residues which are linked directly to the 2' and /or 3' hydroxyls of the furanose or carbocycle via a carbon atom according to Formula II, or linked directly to two of the 2' and 3' hydroxyls of the furanose or carbocycle via a common carbon atom according to Formula III,

Formula II



wherein:

O is the corresponding 2' and/or 3' oxygen of the furanose or carbocycle;

C is a carbon atom;

R_5, R_6, and R_7 are H, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, such that the moiety defined according to Formula II is an ether; or

R_5 and R_6 are H, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, and R_7 is alkoxy, cycloalkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy such that the moiety defined according to formula II is an acyclic acetal or ketal; or

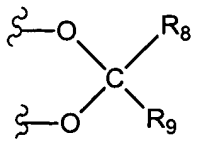
R_5 and R_6 are taken together as oxygen or sulfur doubly bonded to C, and R_7 is alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, such that the moiety defined according to Formula II is an ester or thioester; or

R_5 and R_6 are taken together as oxygen or sulfur doubly bonded to C, and R_7 is amino or mono- or disubstituted amino, where the substituents are alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, such that the moiety according to Formula II is a carbamate or thiocarbamate; or

R_5 and R_6 are taken together to mean oxygen or sulfur doubly bonded to C, and R_7 is alkoxy, cycloalkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy, such that the moiety according to Formula II is a carbonate or thiocarbonate; or

R_7 is not present and R_5 and R_6 are taken together as oxygen or sulfur doubly bonded to C and both the 2' and 3' oxygens of the furanose are directly bound to C to form a cyclical carbonate or thiocarbonate;

Formula III



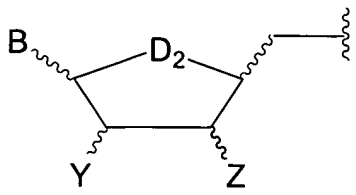
wherein:

the two O-groups are the 2' and 3' oxygens of the furanose or carbocycle; and the 2' and 3' oxygens of the furanose or carbocycle are linked by the common carbon atom to form a cyclical acetal, cyclical ketal, or cyclical orthoester; and

for cyclical acetals and ketals, R_8 and R_9 are independently hydrogen, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, substituted aryl, or may be joined together to form a homocyclic or heterocyclic ring composed of 3 to 8 atoms, or

for cyclical orthoesters, R_8 is hydrogen, alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl, R_9 is alkyloxy, cycloalkyloxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy;

A is a nucleoside residue defined as:



and linked to the phosphate chain via the 5' position of the furanose or carbocycle; wherein:

D_2 =O or CH_2;

Z =H, OH, or OR_3;

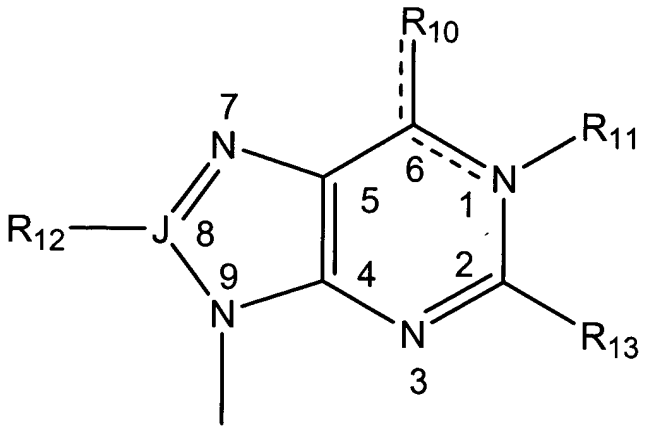
Y =H, OH, or OR_4;

R_3 and R_4 are residues which are linked directly to the 2' and /or 3' hydroxyls of the furanose or carbocycle via a carbon atom according to Formula II, or linked directly to two of the

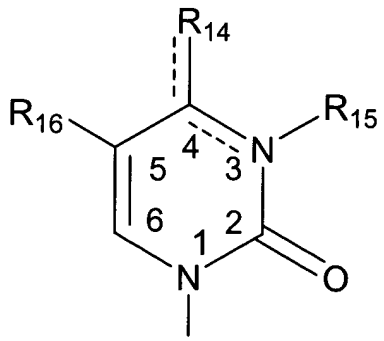
2' and 3' hydroxyls of the furanose or carbocycle via the common carbon atom according to Formula III;

B and B' are independently a purine or a pyrimidine residue according to general Formulae IV and V which is linked to the 1' position of the furanose or carbocycle via the 9- or 1- position of the base, respectively;

Formula IV



Formula V



wherein:

R_{10} and R_{14} are hydroxy, oxo, amino, mercapto, alkylthio, alkyloxy, aryloxy, alkylamino, cycloalkylamino, aralkylamino, arylamino, diaralkylamino, diarylamino, or dialkylamino, where the alkyl groups are optionally linked to form a heterocycle; or

R_{10} and R_{14} are acylamino~~, provided that they incorporate an amino residue from the C-6~~

~~position of the purine or the C-4 position of the pyrimidine~~; or

when R_{10} in a purine or R_{14} in a pyrimidine has as its first atom nitrogen, R_{10} and R_{11} or R_{14} and R_{15} are taken together to form a 5-membered fused imidazole ring, optionally substituted on the etheno ring with alkyl, cycloalkyl, aralkyl, or aryl moieties, as described for R_5-R_9 above;

J is carbon or nitrogen, with the provision that when nitrogen, R_{12} is not present;

R_{11} is hydrogen, O, or is absent;

R_{15} is hydrogen, or acyl;

R_{12} is hydrogen, alkyl, azido, alkylamino, arylamino or aralkylamino, alkoxy, aryloxy or aralkyloxy, alkylthio, arythio or aralkylthio, or ω-A(C_{1-6}alkyl)B-, wherein A and B are independently amino, mercapto, hydroxy or carboxyl; and

R_{13} is hydrogen, chlorine, amino, monosubstituted amino, disubstituted amino, alkylthio, arylthio, or aralkylthio, where the substituent on sulfur contains up to a maximum of 20 carbon atoms, with or without unsaturation; and

R16 is hydrogen, methyl, alkyl, halo, alkyl, alkenyl, substituted alkenyl, alkynyl, or substituted alkynyl.

4. (Previous Presented) The method according to Claim 3, wherein said pharmaceutical composition reduces the incidence of dose-related adverse side effects of other therapeutic agents that are used to prevent, manage or treat platelet aggregation disorders.

5. (Previous Presented) The method according to Claim 3, wherein said diseases or conditions associated with platelet aggregation are disorders or procedures characterized by thrombosis, primary arterial thrombotic complications of atherosclerotic disease, thrombotic complications of interventions of atherosclerotic disease, thrombotic complications of surgical or mechanical damage, mechanically-induced platelet activation, shunt occlusion, thrombosis secondary to vascular damage and inflammation, indications with a diffuse thrombotic/platelet consumption component, venous thrombosis, coronary arterial thrombosis, pathological effects of atherosclerosis and arteriosclerosis, platelet aggregation and clot formation in blood and blood products during storage, chronic or acute states of hyper-aggregability, reocclusion of an artery or vein following fibrinolytic therapy, platelet adhesion associated with extracorporeal circulation,

thrombotic complications associated with thrombolytic therapy, thrombotic complications associated with coronary and other angioplasty, or thrombotic complications associated with coronary artery bypass procedures.

6. (Previous Presented) The method according to Claim 5, wherein said disorders or procedures associated with thrombosis are unstable angina, coronary angioplasty, and myocardial infarction; said primary arterial thrombotic complications of atherosclerosis are thrombotic stroke, peripheral vascular disease, and myocardial infarction without thrombolysis; said thrombotic complications of interventions of atherosclerotic disease are angioplasty, endarterectomy, stent placement, coronary and other vascular graft surgery; said thrombotic complications of surgical or mechanical damage are tissue salvage following surgical or accidental trauma, reconstructive surgery; said mechanically – induced platelet activation is caused by cardiopulmonary bypass resulting in microthromboembolism during storage of blood products; said shunt occlusion is renal dialysis and plasmapheresis; said thromboses secondary to vascular damage and inflammation are found in vasculitis, arteritis, glomerulonephritis and organ graft rejection; said indications with a diffuse thrombotic/platelet consumption component are disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, heparin-induced thrombocytopenia, and pre-eclampsia/eclampsia; said venous thrombosis are deep vein thrombosis, veno-occlusive disease, hematological conditions, and migraine; and said coronary arterial thrombosis is associated with unstable angina, coronary angioplasty or acute myocardial infarction.

7. (Original) The method according to Claim 6, wherein said hematological conditions are thrombocythemia and polycythemia.

8. (Previous Presented) The method according to Claim 5, wherein said pathological effects of atherosclerosis and arteriosclerosis are arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina, transient ischemic attacks, and strokes, peripheral vascular disease, arterial thrombosis, preeclampsia, embolism, restenosis or abrupt closure following angioplasty, carotid endarterectomy, and anastomosis of vascular grafts; said chronic or acute

states of hyper-aggregability is caused by DIC, septicemia, surgical or infectious shock, post-operative and post-partum trauma, cardiopulmonary bypass surgery, incompatible blood transfusion, abruptio placenta, thrombotic thrombocytopenic purpura, snake venom and immune diseases; and said reocclusion of an artery or vein following fibrinolytic therapy is inhibited by internal administration of said compound with a fibrinolytic agent.

9. (Original) The method according to Claim 8, wherein said fibrinolytic agent is a natural or synthetic product which directly or indirectly causes lysis of a fibrin clot.

10. (Original) The method according to Claim 8, wherein said fibrinolytic agent is a plasminogen activator selected from the group consisting of anistreplase, urokinase, pro-urokinase, streptokinase, tissue plasminogen activator and mutants, or variants thereof, which retain plasminogen activator activity.

11. (Original) The method according to Claim 10, wherein said variants are selected from the group consisting of variants which have been chemically modified, variants which one or more amino acids have been added, deleted or substituted, and variants with one or more modified functional domains.

12. (Previous Presented) The method according to Claim 11, wherein said modified functional domains are added, deleted or altered by combining the active site of one plasminogen activator with the fibrin binding domain of another plasminogen activator or fibrin binding molecule.

13. (Previous Presented) The method according to Claim 3, wherein said administering is systemic administration of said compound to a subject.

14. (Original) The method according to Claim 13, wherein said systemic administration is an administration selected from the group consisting of: injecting an injectable form of said

compound; administering by mouth an oral form of said compound; applying to the skin a transdermal patch or a transdermal pad containing said compound; administering a liquid/liquid suspension of said compound via nose drops or nasal spray; administering a nebulized liquid of said compound to oral or nasopharyngeal airways; administering rectally a suppository form of said compound; administering vaginally said compound in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles; administering said compound intravitreally; and administering via intra-operative instillation a gel, cream, powder, foam, crystals, liposomes, spray or liquid suspension form of said compound; such that a therapeutically effective amount of said compound contacts the target platelets of said patient via systemic absorption and circulation.

15. (Original) The method according to Claim 13, wherein said systemic administration comprises infusion of said compound to target platelets via a device selected from the group consisting of a pump catheter system and a continuous or selective release device.

16 – 21 (Canceled)

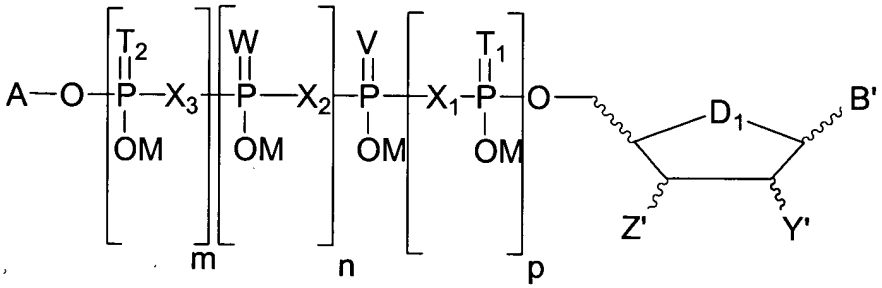
22. (Previous Presented) The method according to Claim 3, wherein said $P2Y_{12}$ receptor antagonist compound is selected from the group consisting of: di[3'(phenylcarbamate)dUp2dU]; 2',3' phenylacetaldehyde acetal Up3U; di 2',3' phenylacetaldehyde acetal Up3U; 2',3' phenylacetaldehyde acetal Up4A; 2',3' phenylacetaldehyde acetal Ap4U; di 2',3' phenylacetaldehyde acetal Ap4U; 2',3' phenylacetaldehyde acetal Ip4U; 2',3' phenylacetaldehyde acetal Up4U; 2',3' phenylacetaldehyde acetal Ip4U; 2',3' phenylacetaldehyde acetal Up4dC; tetraphenylcarbamate Up4U; di 2',3' benzaldehyde acetal Ip4U; di 2',3' benzaldehyde acetal Up4U; 2',3' benzaldehyde acetal Up4U; di 2',3' phenylacetaldehyde acetal Cp4U; 2',3' phenylacetaldehyde acetal Cp4U; 2',3' phenylacetaldehyde acetal Up4C; 2',3' phenylacetaldehyde acetal Up4T; di 2',3' benzaldehyde acetal Cp4U; 2',3' benzaldehyde acetal Ip4U; 2',3' benzaldehyde acetal Up4U; 2',3' benzaldehyde acetal Up4dC; 2',3' benzaldehyde acetal Cp4U; 2',3' benzaldehyde acetal Up4C;

2',3' phenylpropionaldehyde acetal Up4U; di 2',3' phenylpropionaldehyde acetal Up4U; 2',3' benzaldehyde acetal Cp4C; bis MANT Up4U; Mant Up4U, di 2'/3' benzylacetal Up4U; mono 2'/3' benzylacetal Up4U; triphenyl carbamate Up4U; 2',3' phenylcarbamate Up4U; and monophenylcarbarnate Up4U.

23. (Previous Presented) The method according to Claim 3, wherein said $P2Y_{12}$ receptor antagonist compound is P^1-[2-(3-trifluoromethylpropyl)thio-6-(2-methylthio)ethylamino 2', 3'-(benzyl)methylene dioxy purine riboside]-P^4-(2',3'-(benzyl)methylene dioxy uridine)tetraphosphate.

24. (Previous Presented) The method according to Claim 3, wherein said $P2Y_{12}$ receptor antagonist compound is a dinucleotide compound of Formula I:

Formula I



wherein:

X_1, X_2, X_3, T_1, T_2, W, and V are oxygen;

m= 0;

n= 0 or 1;

p= 0, 1, or 2;

D_1 =O;

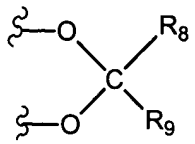
Y' = OR_1;

Z' = OR_2; and

R_1 and R_2 are residues which are linked directly to the 2' and 3' hydroxyls of the furanose via a

common carbon atom according to Formula III,

Formula III



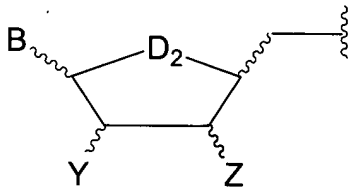
wherein:

the two O-groups are the 2' and 3' oxygens of the furanose; and the 2' and 3' oxygens of the furanose are linked by the common carbon atom to form a cyclical acetal;

R_8 is hydrogen;

R_9 is alkyl, cycloalkyl, aralkyl, aryl, substituted aralkyl, or substituted aryl;

A is a nucleoside residue defined as:



which is linked to the phosphate chain via the 5' position of the furanose; wherein:

D_2 =O;

Z = OR_3;

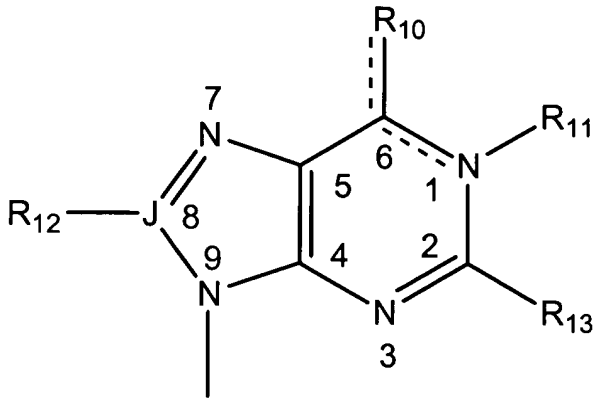
Y = OR_4; and

R_3 and R_4 are residues which are linked directly to the 2' and 3' hydroxyls of the furanose via the common carbon atom according to Formula III to form a cyclical acetal;

B' and B independently are purine residues according to general Formula IV which are

linked to the 1' position of each respective furanose via the 9-position of the respective base;

Formula IV



wherein:

R_{10} is amino, alkylamino, cycloalkylamino, aralkylamino, arylamino, diaralkylamino, diarylamino, or dialkylamino, where the alkyl groups are optionally linked to form a heterocycle; or

R_{10} is acylamino~~, provided that it incorporates an amino residue from the C-6 position of the purine~~;

J is carbon;

R_{11} is hydrogen or is absent;

R_{12} is hydrogen, alkyl, azido, alkylamino, arylamino, aralkylamino, alkoxy, aryloxy, aralkyloxy, alkylthio, arythio or aralkylthio; and

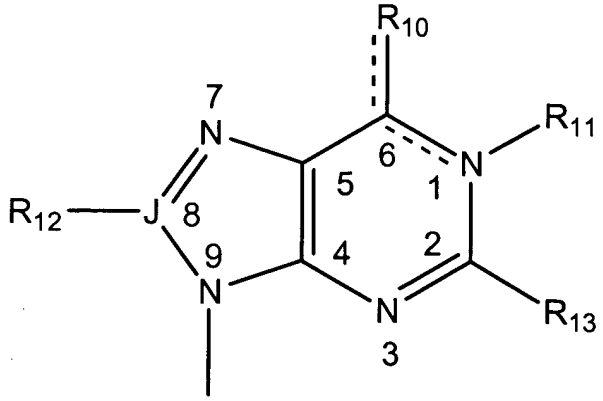
R_{13} is hydrogen, chlorine, amino, monosubstituted amino, disubstituted amino, alkylthio, arylthio, or aralkylthio, where the substituent on sulfur contains up to a maximum of 20 carbon atoms, with or without unsaturation.

25. (Previous Presented) The method according to Claim 24, wherein:

R_9 is aralkyl, aryl, substituted aralkyl, or substituted aryl;

B' and B independently are purine residues according to general Formula IV which are linked to the 1' position of each respective furanose via the 9-position of the respective base;

Formula IV



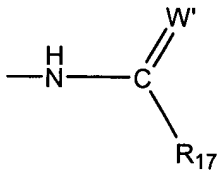
wherein:

R_{12} is hydrogen;

R_{13} is hydrogen or chlorine; and

R_{10} is acylamino according to Formula VI~~, provided that it incorporates an amino residue from the C-6 position of the purine~~;

Formula VI



wherein:

NH is the amino residue at the C-6 position of a said purine;

C is a carbon atom;

W' is oxygen or sulfur; and

R_{17} is amino or mono- or disubstituted amino such that the moiety according to Formula VI is a urea or thiourea; or

R_{17} is alkoxy, aralkyloxy, aryloxy, substituted aralkyloxy, or substituted aryloxy, such that the moiety according to Formula VI is a carbamate or thiocarbamate.